UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

30/MAR/2011

MEMORANDUM

Subject:	Name of Pesticide Product:	DuPont™ Advion® Cockroach Gel Bait
	EPA File Symbol:	352-652
	DP Barcode:	D385252
	Decision No.:	442999
	Action Code:	R340
	PC Code:	067710 Indoxacarb

From: Rick J. Whiting, Biologist
Science Information Management Branch (SIMB)
Health Effects Division (7509P)

R. Whiting
Byron T. Boland
MARCH-30-2011

To: Jennifer Urbanski / John Herbert, RM Team 07
Insecticide-Rodenticide Branch
Registration Division (7505P)

Applicant: E.I. Du Pont de Nemours and Company
1700 Market Place
Wilmington, DE 19898

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt
067710 Indoxacarb (CAS No. 173584-44-6)	0.6
Inert Ingredient(s):	99.4
Total:	100.0%

ACTION REQUESTED: The Risk Manager requests: "Attn Acute Tox Reviewer: Please review attached acute tox data to determine if the registrant can change the basic formulation. For your review, I attached the proposed CSF, the label, the cover letter and 5 MRIDs."

BACKGROUND: E.I. Du Pont de Nemours and Company has submitted five acute toxicity studies (oral, dermal, primary eye irritation, primary dermal irritation and dermal sensitization), a Basic Formulation CSF dated December 7, 2010 and a proposed label for DuPont™ Advion® Cockroach Gel Bait, EPA Reg. No. 352-652 . The acute oral and dermal toxicity studies were conducted at E.I. du Pont de Nemours and Co., DuPont Haskell Global Centers for Health & Environmental Sciences and were assigned MRID numbers 48317403 and 48317404. The primary eye and dermal irritation studies and the dermal sensitization study were conducted at Eurofins PSL and were assigned MRID numbers 48317405, 48317406 and 48317407.

To support the registration EPA Reg. No. 352-652 in 2005, E.I. Du Pont de Nemours and Company submitted five acute toxicity studies. These studies were reviewed by B. Backus (D312433; EPA File Symbol 352-ALE; 01/FEB/2005) and the following acute toxicity profile was generated.

Acute oral toxicity	IV	Acceptable	MRID 46450503
Acute dermal toxicity	IV	Acceptable	MRID 46450504
Acute inhalation toxicity	IV	Waived*	
Primary eye irritation	IV	Acceptable	MRID 46450505
Primary dermal irritation	IV	Acceptable	MRID 46450506
Dermal sensitization	Negative	Acceptable	MRID 46450507

* From the B. Backus memorandum: "Based on the physical form (a gel) of this product, the low percentage (0.6%) of active ingredient, and the low (toxicity category IV) inhalation toxicity of the manufacturing use product (52.7% active) TRB concludes that a waiver of the inhalation study requirement for 352-ALE is appropriate and that this formulation can be assigned to EPA Toxicity Category IV in terms of its inhalation exposure hazard potential."

In a letter to EPA dated December 8, 2010, the registrant explained that the five new acute toxicity studies have been submitted to EPA because the Basic Formulation for 352-652 has been revised.

COMMENTS AND RECOMMENDATIONS:

1. The five studies have been reviewed and are classified as Acceptable.

2. The new acute toxicity profile for DuPont™ Advion® Cockroach Gel Bait, EPA Reg. No. 352-652, is as follows:

Acute oral toxicity	IV	Acceptable	MRID 48317403
Acute dermal toxicity	IV	Acceptable	MRID 48317404
Acute inhalation toxicity	IV	Waived	
Primary eye irritation	IV	Acceptable	MRID 48317405
Primary dermal irritation	IV	Acceptable	MRID 48317406
Dermal sensitization	Positive	Acceptable	MRID 48317407

3. Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System:

PRODUCT ID #: 000352-00652

PRODUCT NAME: DUPONT ADVION COCKROACH GEL BAIT

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

First Aid: [Not required. Registrant can use Category III statements]

4. In addition, EPA noted that the registrant has included additional Precautionary statements. EPA finds this additional labeling information acceptable.

5. The Basic Formulation CSF dated December 7, 2010 for the proposed product should also be reviewed and accepted by the TRB Product Chemistry Team.

Reviewer: Rick J. Whiting **Date: March 30, 2011**
Risk Manager (EPA): 07

STUDY TYPE: Acute Oral Toxicity - Rat; OCSPP 870.1100; OECD 425

TEST MATERIAL: Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid)

CITATION: Carpenter, C. (2010) Indoxacarb (DPX-MP062) 0.6RB Gel: Acute Oral Toxicity Study in Rats- Up and-Down Procedure. Project Number: DuPont-30706. Unpublished study prepared by E.I. du Pont de Nemours and Company. 26 p. August 6, 2010. MRID 48317403

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, DE 19898

EXECUTIVE SUMMARY: In an acute oral toxicity study (Up-and Down Procedure; MRID 48317403), three young adult female Crl:CD(SD) rats (age: 11 weeks; body weight: 207.8-232.0 g; source: Charles River Laboratories, Inc., Raleigh, NC) were given a single oral dose of Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid) suspended in 0.5% aqueous methylcellulose at a dose of 5000 mg/kg bw by gavage. The rats were dosed at a volume of 10 mL/kg. One rat was initially dosed and the remaining two animals were simultaneously dosed four days later. The rats were fasted approximately 17 hours prior to dosing.

Observations for mortality and signs of illness, injury, or abnormal behavior were made daily throughout the study. The rats were observed for clinical signs at the beginning of fasting, just before dosing, once during the first 30 minutes after dosing and two more times on the day of dosing, and once daily thereafter. The rats were weighed on test days -1, 0, 7 and 14. On test day 14, the rats were euthanized and necropsied.

All animals survived and gained body weight during the study. No clinical signs were observed during the study. No gross abnormalities were noted for any of the animals necropsied at the conclusion of the 14-day observation period.

Oral LD_{50} Females > 5000 mg/kg bw

Based on the Oral LD_{50} in females, Indoxacarb 0.6RB is classified as EPA Toxicity Category IV.

This acute oral study is classified as Acceptable. It does satisfy the guideline requirement for an acute oral study (OCSPP 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Individual animals were dosed as follows:

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Test/Substance: Indoxacarb 0.6RB
Test type: Limit Test
Limit dose (mg/kg): 5000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	2046	5000	O	O
2	43	5000	O	O
3	2048	5000	O	O

(X = Died, O = Survived)

Dose Recommendation: The limit test is complete.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
5000	3	0	3
All Doses	3	0	3

Statistical Estimates:

The LD50 is greater than 5000 mg/kg.

Limit Test

Dosing Sequence	Animal No.	Dose level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	2046	5000	S	S
2	43	5000	S	S
3	2048	5000	S	S

S = survival D = death

Statistics: Acute Oral Toxicity (Guideline 425) Statistical Program (Westat, version 1.0, May 2001) was used for all data analyses including: dose progression selections, stopping criteria determinations and/or LD_{50} and confidence limit calculations.

A. Mortality: There was no mortality.

B. Body weights: All animal gained body weight over the 14-day observation period.

C. Clinical observations: No clinical signs were observed during the study.

D. Gross Necropsy: No gross abnormalities were noted for any of the animals necropsied at the conclusion of the 14-day observation period. On page 13 of the study, the study author states "Discolored (red) thymus observed in 1 rat was nonspecific and is a common finding in rats of this strain and age."

E. Reviewer's Conclusions: EPA agrees with the study author regarding the acute oral LD_{50}. Indoxacarb 0.6RB is classified as EPA Toxicity Category IV.

F. Deficiencies: None.

Reviewer: Rick J. Whiting **Date: March 30, 2011**
Risk Manager (EPA): 07

STUDY TYPE: Acute Dermal Toxicity - Rat; OCSPP 870.1200; OECD 402

TEST MATERIAL: Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid)

CITATION: Carpenter, C. (2010) Indoxacarb (DPX-MP062) 0.6RB Gel: Acute Dermal Toxicity Study in Rats. Project Number: DuPont-30707. Unpublished study prepared by E.I. du Pont de Nemours and Company. 33 p. August 6, 2010. MRID 48317404

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, DE 19898

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 48317404), five male and five female young adult Crl:CD(SD) rats (age: approximately 9 weeks; body weight: 301.4-341.4 g for males and 215.2-229.3 g for females; source: Charles River Laboratories, Inc., Raleigh, NC) were dermally exposed on a clipped scapular to the lumbar region for 24 hours to 5000 mg/kg bw of Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid). The area to be treated (approximately 5 cm x 7.4 cm) was marked on the dorsal skin of each rat with a water-insoluble marker. The aliquot of test material was spread evenly, directly on the skin, covering an area of approximately 37 cm^2 (equal to approximately 10% of the total body surface area) and covered with a gauze patch. The rats were wrapped with stretch gauze bandage and self-adhesive bandage. The test material is a paste-like solid and made contact with the skin without moistening it with a vehicle. After the exposure period, the wrappings were removed and the excess test material was removed with warm water and the skin dried. Dermal effects were scored according to the Draize Scale (1959). Individual body weights were recorded prior to test material application and again on Days 7 and 14. Observations for mortality, signs of illness, injury, abnormal behavior clinical signs of toxicity and dermal irritation were made daily throughout the study (weekends excluded for dermal irritation). Gross necropsies were performed on all animals.

There were no deaths. All male and four female animals gained weight during the study. One female animal lost body weight between Day 7 and 14. No clinical signs were observed during the study. No dermal irritation was noted for 2 males and 4 females. Erythema (score of 1) was observed at 3 male test sites on Day 1 with clearance by Day 2. Erythema (score of 1) was also observed at 1 female test site on Day 4 and hyperkeratosis and epidermal scaling was present on Days 4, 5 and 6. Irritation had cleared by Day 7. No gross abnormalities were noted for any of the animals necropsied at the conclusion of the 14-day observation period.

Dermal LD_{50} Males > 5000 mg/kg bw
Dermal LD_{50} Females > 5000 mg/kg bw
Dermal LD_{50} Combined > 5000 mg/kg bw

Based on the LD_{50}, Indoxacarb 0.6RB is classified as EPA Toxicity Category IV.

This acute dermal study is classified Acceptable. It does satisfy the guideline requirement for an acute dermal study (OCSPP 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

A. Mortality: There were no deaths.

B. Body weights: All male and four female animals gained weight during the study. One female animal lost body weight between Day 7 and 14.

C. Clinical observations: No clinical signs were observed during the study.

D. Dermal irritation: No dermal irritation was noted for 2 males and 4 females. Erythema (score of 1) was observed at 3 male test sites on Day 1 with clearance by Day 2. Erythema (score of 1) was also observed at 1 female test site on Day 4 and hyperkeratosis and epidermal scaling was present on Days 4, 5 and 6. Irritation had cleared by Day 7.

E. Gross necropsy: No gross abnormalities were noted for any of the animals necropsied at the conclusion of the 14-day observation period.

F. Reviewer's Conclusions: EPA agrees with the study author regarding the acute dermal LD_{50}. Indoxacarb 0.6RB is classified as EPA Toxicity Category IV.

G. Deficiencies: None.

Reviewer: Rick J. Whiting **Date: March 30, 2011**
Risk Manager (EPA): 07

STUDY TYPE: Primary Eye Irritation - Rabbit; OCSPP 870.2400; OECD 405

TEST MATERIAL: Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid)

CITATION: Lowe, C. (2010) Indoxacarb (DPX-MP062) 0.6RB Gel: Primary Eye Irritation in Rabbits. Project Number: DuPont-30708, EPSL Study No. 29983. Unpublished study prepared by Eurofins/Product Safety Laboratories. 21 p. September 20, 2010. MRID 48317405

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, DE 19898

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 48317405), 0.1 mL of Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid) was instilled into the conjunctival sac of the right eye of three young adult female New Zealand White rabbits (weight: 2296 – 2456 g; source: Robinson Services, Inc., Clemmons, NC). The other untreated eye served as a control. Prior to use, the test material was backloaded into a syringe. Prior to instillation, 2-3 drops of ocular anesthetic (Tetracaine Hydrochloride Ophthalmic Solution, 0.5%) were placed into both the treated and the control eye of each animal. Ocular irritation was evaluated using a high-intensity white light in accordance with Draize *et al.* (1944) at 1, 24, 48 and 72 hours post-instillation.

No corneal opacity or iritis was noted in any treated eye during the study. Conjunctival redness (score of 2) was noted in one rabbit at 1 hour. Conjunctival redness (score of 1) was noted in two rabbits at 1 hour and in one rabbit at 24 hours. Conjunctival chemosis (score of 1) was noted in two rabbits at 1 hour. Conjunctival discharge, one rabbit with a score of 2 and two rabbits with a score of 1, was noted at 1 hour. All ocular irritation was resolved by 48 hours. No "positive" scores were noted at 24 hours. The Maximum Mean Total Score (MMTS) was 6.33, recorded 1 hour hours after test material instillation.

In this study, the formulation was minimally irritating. Indoxacarb 0.6RB is classified as EPA Toxicity Category IV for primary eye irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OCSPP 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

A. Observations: No corneal opacity or iritis was noted in any treated eye during the study. Conjunctival redness (score of 2) was noted in one rabbit at 1 hour. Conjunctival redness (score of 1) was noted in two rabbits at 1 hour and in one rabbit at 24 hours. Conjunctival chemosis (score of 1) was noted in two rabbits at 1 hour. Conjunctival discharge, one rabbit with a score of 2 and two rabbits with a score of 1, was noted at 1 hour. All ocular irritation was resolved by 48 hours. No "positive" scores were noted at 24 hours.

Individual Scores for Ocular Irritation

READING	RABBIT NUMBER	CORNEAL OPACITY	IRITIS	CONJUNCTIVA*		
				Redness	Chemosis	Discharge
1 Hour	3401	0	0	1	0	2
	3402	0	0	2	1	1
	3403	0	0	1	1	1
24 Hours	3401	0	0	0	0	0
	3402	0	0	1	0	0
	3403	0	0	0	0	0
48 Hours	3401	0	0	0	0	0
	3402	0	0	0	0	0
	3403	0	0	0	0	0
72 Hours	3401	0	0	0	0	0
	3402	0	0	0	0	0
	3403	0	0	0	0	0

*Score of 2 or more required to be considered "positive."

The incidence of positive effects, severity and reversibility are detailed below:

Time Post Instillation	Incidence of Positive Effects		
	Corneal Opacity	Iritis	Conjunctivitis
1 Hour	0/3	0/3	2/3
24 Hours	0/3	0/3	0/3
48 Hours	0/3	0/3	0/3
72 Hours	0/3	0/3	0/3

B. Results: Indoxacarb 0.6RB was minimally irritating. The Maximum Mean Total Score (MMTS) was 6.33, recorded 1 hour hours after test material instillation.

C. Reviewer's Conclusions: EPA agrees with the study author's conclusions. Indoxacarb 0.6RB is classified as EPA Toxicity Category IV.

D. Deficiencies: None.

Reviewer: Rick J. Whiting **Date: March 30, 2011**
Risk Manager (EPA): 07

STUDY TYPE: Primary Dermal Irritation - Rabbit; OCSPP 870.2500; OECD 404

TEST MATERIAL: Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid)

CITATION: Lowe, C. (2010) Indoxacarb (DPX-MP062) 0.6RB Gel: Primary Skin Irritation in Rabbits. Project Number: DuPont-30709, EPSL Study No. 29984. Unpublished study prepared by Eurofins/Product Safety Laboratories. 21 p. September 20, 2010. MRID 48317406

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, DE 19898

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 48317406), three young female adult New Zealand White rabbits (weight: 2030 – 2420 g; source: Robinson Services, Inc., Clemmons, NC) were dermally exposed to Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid). At the request of the sponsor, the study was conducted in a stepwise manner using a single patch applied initially to one rabbit for 4 hours. Five-tenths of a milliliter of the test material as received was applied to one 6 cm^2 intact dose site on each animal and covered with a 1-inch x 1-inch, 4-ply gauze pad. The pad and trunk were wrapped with semi-occlusive Micropore tape. Elizabethan collars were placed on the rabbits. After 4 hours of exposure, the pads and collars were removed and the test sites were gently cleansed of any residual test material. Individual test sites were scored according to the Draize scoring system (1944) at approximately 30-60 minutes, 24, 48, and 72 hours and/or Day 7 after patch removal.

Very slight (score of 1; 1/3 sites) to well-defined (score of 2; 1/3 sites) erythema was observed at one hour. Very slight erythema was noted at 1/3 sites at 24, 48 and 72 hours. Very slight (score of 1) edema was noted at 1/3 sites at one hour. All dermal irritation was resolved by Day 7.

In this study, the formulation was slightly irritating. Indoxacarb 0.6RB is classified as EPA Toxicity Category IV for primary dermal irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OCSPP 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

A. Observations: Very slight (score of 1; 1/3 sites) to well-defined (score of 2; 1/3 sites) erythema was observed at one hour. Very slight erythema was noted at 1/3 sites at 24, 48 and 72 hours. Very slight (score of 1) edema was noted at 1/3 sites at one hour. All dermal irritation was resolved by Day 7.

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

Animal No.	Sex	Hours After Patch Removal				Days
		1	24	48	72	7
3501	F	0/0	0/0	0/0	0/0	--
3502	F	2/1	1/0	1/0	1/0	0/0
3503	F	1/0	0/0	0/0	0/0	0/0

B. Results: The Primary Dermal Irritation Index (PDII) is 0.58 based dermal irritation scores from 1 hour to 72 hours.

C. Reviewer's Conclusions: EPA noted a discrepancy within the study report. On pages 10 and 16 the study authors state that "There was no edema noted for any treated dose site during the study." However on page 18, the data from Table 2: Individual Skin Irritation Scores, indicates that animal number 3502 had a score of 1 for edema at 1 hour. EPA has included this score in the calculation of the PDII and overall assessment of this study.

Based on the results of this study, Indoxacarb 0.6RB was considered to be slightly irritating and was classified as Toxicity Category IV.

D. Deficiencies: None.

Reviewer: Rick J. Whiting **Date: March 30, 2011**
Risk Manager (EPA): 07

STUDY TYPE: Dermal Sensitization - Guinea Pig; OCSPP 870.2600; OECD 406, 429

TEST MATERIAL: Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid)

CITATION: Lowe, C. (2010) Indoxacarb (DPX-MP062) 0.6RB Gel: Dermal Sensitization Magnusson- Kligman Maximization Method. Project Number: DuPont-30710, EPSL Study No. 29985. Unpublished study prepared by Eurofins/Product Safety Laboratories. 33 p. September 21, 2010. MRID 48317407

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, DE 19898

EXECUTIVE SUMMARY: A Magnusson-Kligman maximization test (MRID 48317407) was conducted with young adult male Hartley albino guinea pigs (weight: 247-386 g; source: Elm Hill Breeding Labs, Chelmsford, MA) to determine the potential for Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid) to invoke dermal skin sensitization reactions. The study was conducted using four stages; preliminary irritation screens, a two-stage induction phase, and a challenge phase as described below.

Preliminary irritation testing was performed on 12 animals to determine appropriate concentrations of the test material that could be used for both intradermal and topical induction as well as topical challenge. An emulsion of 50% v/v Freund's Adjuvant Complete in distilled water was used during the intradermal injection and the injection induction phases. This emulsion was thoroughly mixed using a stir plate.

The first induction phase involved six intradermal injections into the suprascapular area of each of 20 guinea pigs. These doses were comprised of pairs of injections of the test material in propylene glycol (5% w/w), the test material (5% w/w) combined with an emulsion of Freund's Adjuvant Complete, as well as an emulsion of Freund's Adjuvant Complete alone. A sham control group (ten animals) was maintained under the same environmental conditions and received injections of propylene glycol, propylene glycol (50% w/w) combined with an emulsion of Freund's Adjuvant Complete, as well as an emulsion of Freund's Adjuvant Complete alone. Approximately 24 and 48 hours after the injections, all sites were evaluated for an irritation response (erythema).

Approximately one week later, the second phase of induction was conducted. The test material (test group) or distilled water (test vehicle control group) was then applied topically for a period of 48 hours to the area encompassing the intradermal injection sites. Approximately one hour after the topical induction patches were removed, all animals were scored for erythema.

Approximately two weeks later, a primary challenge consisting of three occluded applications was conducted on each animal. One Hill Top Chamber containing 0.5 ml of propylene glycol was applied to a naive site on the left middle flank of each animal. The remaining two Hill Top Chambers containing 0.5 grams of the HNIC (Highest Non-Irritating Concentration, determined in the preliminary irritation screen to be 100%) of the test material and 0.5 ml of a 33% dilution

of the HNIC (33% w/w mixture in propylene glycol) were positioned on two naive sites on the right front and rear flank, respectively, for approximately 24 hours. The test vehicle control group was also treated with the test substance and test vehicle (as described above) at challenge. Approximately 24 and 48 hours after challenge patch removal, all animals were scored for a sensitization response (erythema).

Tables summarizing the incidence and severity of the sensitization response noted after challenge are found below.

	Incidence with Skin Reactions*			
	Test Animals		Test Vehicle Control Animals	
	Hours			
	24	48	24	48
100%	19/20	19/20	0/10	0/10
33% w/w in Ppropylene glycol	20/20	20/20	0/10	0/10
Propylene glycol	0/20	0/20	0/10	0/10

* Animals with scores greater than 0.5

	Severity*			
	Test Animals		Test Vehicle Control Animals	
	Hours			
	24	48	24	48
100%	1.48	1.63	0.15	0.05
33% w/w in Ppropylene glycol	1.95	1.85	0.45	0.15
Propylene glycol	0.00	0.00	0.00	0.00

*Sum of the erythema scores divided by the number of animal evaluated

Based on the results of this study, Indoxacarb 0.6RB is considered to be a dermal sensitizer.

This study is classified as Acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OCSPP 870.2600; OECD 406, 429) in the Guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. PROCEDURE:

A. Preliminary Irritation Testing (from page 13 of the study):

Preliminary Intradermal Injection: Prior to the induction phase, a group of four animals was used to determine the concentration of the test substance which produced faint to moderate irritation via intradermal injection. The fur was removed by clipping the suprascapular region of each guinea pig. This area was divided into six test sites (three sites on each side of the midline) on each animal. Each guinea pig received six intradermal injections (0.1 mL each); three concentrations (1, 3, and 5%) of the test substance in propylene glycol and the same concentrations in an emulsion of Freund's Adjuvant Complete. All preparations in Freund's Adjuvant Complete were thoroughly mixed with a tissue homogenizer (Tissue Misser, Model OM02006) prior to application. Approximately 24 and 48 hours after the injections, each site was evaluated for local reactions (erythema).

Preliminary Topical: Prior to the topical induction, a group of four animals was used to determine the irritation potential of the test substance to be used during the topical induction. The previously clipped flank area of each guinea pig was divided into two sites (one site on each side of the midline). The test substance was applied neat (100%) and also mixed with propylene glycol to yield a w/w concentration of 75%. Each concentration (0.5 g or mL) was applied to a 2 cm x 4 cm, 2-ply gauze patch and placed on one of the two test sites. The patch was covered with plastic wrap and secured in place with non-allergenic Durapore™ adhesive tape to avoid dislocation of the patch and to minimize loss of the test substance. After a 48 hour exposure period, the patches were removed and the test sites were gently cleansed of any residual test substance. One hour after patch removal readings were made of local reactions (erythema).

Highest Non-irritating Concentration (HNIC): Prior to the challenge phase, a group of four animals was used to determine the highest non-irritating concentration. The fur was removed by clipping the flanks of each guinea pig. The test substance was applied neat (100%) and also mixed with propylene glycol to yield w/w concentrations of 75%, 50% and 25%. Each concentration (0.5 g or mL) was applied to an occlusive 25 mm Hill Top Chamber and applied to the appropriate test site. The sites were wrapped with nonallergenic Durapore™ adhesive tape. After 24 hours of exposure, the chambers were removed and the test sites were gently cleansed of any residual test substance. Approximately 24 and 48 hours after patch removal, each site was evaluated for local reactions (erythema).

Based on these findings, the concentration which produced faint to moderate irritation (1-2) selected for the intradermal induction was a 5% w/w mixture in propylene glycol. That which produced very faint to moderate irritation (0.5-2) selected for the topical induction was 100%. The HNIC selected for the challenge phase was 100%.

B. Induction Phase (from page 14 of the study):

Intradermal Phase: On the first day of the induction period, the test animals received six intradermal injections (0.1 ml each) in the shaved suprascapular region as follows:

Injection Site No.		Material Injected
Left Upper Back	Right Upper Back	
1	2	Emulsion of Freund's Adjuvant Complete (50% v/v in distilled water)
3	4	5% w/w mixture of test substance in propylene glycol
5	6	5% w/w mixture of test substance in an emulsion of Freund's Adjuvant Complete (50% v/v in distilled water)

The test vehicle control group animals received six intradermal injections (0.1 ml each) in the clipped suprascapular region as follows:

Injection Site No.		Material Injected
Left Upper Back	Right Upper Back	
1	2	Emulsion of Freund's Adjuvant Complete (50% v/v in distilled water)
3	4	100% propylene glycol
5	6	50% w/w mixture of propylene glycol in an emulsion of Freund's Adjuvant Complete (50% v/v in distilled water)

Approximately 24 and 48 hours after the injections, all the above sites were evaluated for an irritation response (erythema).

Topical Induction Phase: Eight days after the intradermal injections, the topical induction phase was conducted. Five-tenths of a gram of the test substance (100%) was applied to the intradermal injection area using a 2 cm x 4 cm, 2-ply gauze patch. The patch was covered with plastic wrap and secured in place with non-allergenic Durapore™ adhesive tape to avoid dislocation of the patch and to minimize loss of the test substance. After the 48-hour exposure period, the patches were removed and the test sites were gently cleansed of any residual test substance. Approximately one hour after patch removal, readings were made of local reactions (erythema).

The test vehicle control group received the same treatment as described above, using 0.5 ml of distilled water for the topical application.

Challenge Phase (pages 14-15 from the study): On Day 21, the right and left flank of each animal were clipped free of fur. Three occluded topical applications were then placed on all test and test vehicle control group animals using 25 mm Hill Top Chambers. A quantity equal to 0.5 mL of propylene glycol was applied to one chamber and positioned on the right flank. The remaining two chambers containing 0.5 grams of the test substance (100%, HNIC) and 0.5 ml of a 33% w/w mixture in propylene glycol (33% dilution of the HNIC) were positioned on the left front and rear flank, respectively. The chambers were wrapped with nonallergenic Durapore™ adhesive tape to avoid dislocation and to prevent evaporation. After the 24 hour exposure period, the chambers were removed and all test sites were gently cleansed of any residual test substance. Approximately 24 and 48 hours after patch removal, these sites were evaluated for a sensitization response (erythema).

II. RESULTS and DISCUSSION:

A. Reactions and duration:

Intradermal Induction Phase (from page 18 of the study):

Test Animals (An emulsion of Freund's Adjuvant Complete [50% v/v in distilled water]): Faint to moderate erythema (1-2) was noted for all test sites 24 and 48 hours after intradermal injections. Blanching was evident at one dose site.

Test Animals (5% w/w mixture of the test substance in propylene glycol): Very faint to moderate erythema (0.5-2) was noted for all test sites 24 and 48 hours after intradermal injections. Blanching and/or dark discoloration was evident at several dose sites.

Test Animals (5% w/w mixture of the test substance in an emulsion of Freund's Adjuvant Complete [50% v/v in distilled water])): Very faint to moderate erythema (0.5-2) was noted for all test sites 24 and/or 48 hours after intradermal injections. Blanching and/or dark discoloration was evident at several dose sites.

Test Vehicle Control Animals (50% w/w mixture of distilled water in an emulsion of Freund's Adjuvant Complete [50% v/v in distilled water])): Faint to moderate erythema (1 -2) was noted for all test vehicle control sites 24 and 48 hours after intradermal injections. Blanching was evident at a few dose sites.

Test Vehicle Control Animals (100% propylene glycol): Very faint to moderate erythema (0.5-2) was noted for all test vehicle control sites at 24 and 48 hours after intradermal injections. Blanching was evident at a most dose sites.

Test Vehicle Control Animals (50% w/w mixture of propylene glycol in an emulsion of Freund's Adjuvant Complete [50% v/v in distilled water])): Very faint to moderate erythema (0.5-2) was noted for all test sites 24 and 48 hours after intradermal injections. Blanching and/or dark discoloration was evident at most dose sites.

Topical Induction Phase (from pages 18-19 of the study):

Test Animals (100% test substance): Faint to moderate erythema (1-2) was noted for all test sites one hour after patch removal.

Test Vehicle Control Animals (100% distilled water): Very faint erythema (0.5) was noted for eight often vehicle control sites one hour after patch removal.

Historical Positive Control Animals (100% HCA): Faint to moderate erythema (1-2) was noted for all positive control sites following the topical induction application.

Historical Sham Control Animals (100% mineral oil): There was no dermal irritation noted for any sham control site following the topical induction application.

Challenge Phase (from page 20 of the study):

Test Animals (100% test substance): Nineteen of twenty test animals exhibited signs of a sensitization response (faint to moderate erythema [1-2]) 24 and 48 hours after challenge patch removal. Very faint erythema (0.5) was present at the remaining site.

Test Vehicle Control Animals (100% test substance): Very faint erythema (0.5) was noted for three often test vehicle control sites 24 hours after challenge. Irritation persisted at one of these sties through 48 hours.

Test Animals (33% w/w mixture of the test substance in propylene glycol): All twenty test animals exhibited signs of a sensitization response (faint to moderate erythema [1 -2]) 24 and 48 hours after challenge patch removal.

Test Vehicle Control Animals (33% w/w mixture of the test substance in propylene glycol): Very faint erythema (0.5) was noted for nine often test vehicle control sites 24 hours after challenge. Irritation persisted at three of these sties through 48 hours.

Test Animals (100% propylene glycol): There was no dermal irritation noted for any test site following challenge.

Test Vehicle Control Animals (100% propylene glycol): There was no dermal irritation noted for any test vehicle control site following the challenge application.

Historical Positive Control Animals (75% w/w mixture of HCA in mineral oil): Nine of ten positive control animals exhibited signs of a sensitization response (faint to moderate erythema [1-2]) 24 hours after challenge patch removal. Similar indications persisted at six of these sites through 48 hours with very faint erythema (0.5) present at all other sites. Desquamation was present at all sites following challenge.

Historical Sham Control Animals (75% w/w mixture of HCA in mineral oil): Very faint erythema (0.5) was noted for all five sham control sites 24 and/or 48 hours after challenge patch removal. Desquamation was present at one site following challenge.

B. Positive control (from page 16 of the study): The procedures used in this study were validated using alpha-Hexylcinnamaldehyde Technical (HCA), as a positive control substance. The induction phases (intradermal and topical) were performed with HCA as a 5% w/w mixture in mineral oil or at 100%. A 75% w/w mixture in mineral oil (HNIC) was used for the challenge phase. The most recent validation, EPSL Study #28477, was performed by EPSL and testing was completed on December 31, 2009. The raw data and report for this study are archived in EPSL Historical Data Notebook No. 04: pages 58-72. This test was conducted at the Dayton, New Jersey facility with HCA using Hartley strain albino guinea pigs from Elm Hill Breeding Labs.

C. Reviewer's Conclusions: EPA agrees with the study author that Indoxacarb 0.6RB is a dermal sensitizer.

D. Deficiencies: None.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D385252
2. **PC CODE:** 067710
3. **CURRENT DATE:** 30/MAR/2011
4. **TEST MATERIAL:** Indoxacarb 0.6RB (Indoxacarb – 0.63% w/w; Lot No. DPX-MP062-603; pH: 5; yellow to tan solid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat E.I. du Pont de Nemours and Co. DuPont-30706 / August 6, 2010	48317403	LD_{50} > 5000 mg/kg (females)	IV	A
Acute dermal toxicity / rat E.I. du Pont de Nemours and Co. DuPont-30707 / August 6, 2010	48317404	LD_{50} > 5000 mg/kg (males and females)	IV	A
Primary eye irritation / rabbit Eurofins PSL DuPont-30708, 29983 September 20, 2010	48317405	Minimally irritating	IV	A
Primary dermal irritation / rabbit Eurofins PSL DuPont-30709, 29984 September 20, 2010	48317406	Slightly irritating	IV	A
Dermal sensitization / guinea pig Eurofins PSL DuPont-30710, 29985 September 21, 2010	48317407	Positive	---	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived